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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,259	07/09/2004	Shunichi Shiozawa	61646 (70904)	7532

21874 7590 04/27/2007

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,259	SHIOZAWA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-3,5,6,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/7/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed on 2/16/2007. Currently claims 4, 7 and 8 are pending. All arguments have been thoroughly reviewed but are not deemed persuasive for the reasons that follow.

Any rejections not reiterated below are hereby withdrawn in view of amendments and arguments.

Objections to claims 4 and 8 have been overcome by amendment. Amended claim 4 is an independent claim. Claim 8 no longer recites "highly possible."

The 102(b) rejection of claim 4 previously of record have been overcome by amendment to the claims to require SEQ ID NO 1 and further having a positive process step relating back to the preamble.

The 102(b) rejection of claim 8 previously of record has been overcome by amendment to the claim to require a whole Angiopoietin-1 gene, including wild-type and mutant. Further the claim now requires the step of evaluating the onset or possible onset of RA.

The 112, 1st paragraph written description with regards to claim 4 has been withdrawn due to amendments. Amended claim 4 now is drawn to SEQ ID No 1, and thus has adequate written description.

The 112, 2nd paragraph rejections with regards to claims 4 and 7 have been withdrawn due to amendments to include a final step.

This action is FINAL.

This action contains new grounds of rejection necessitated by amendment.

Election/Restrictions

2. This application contains claims 1-3, 5-6, 9-10 drawn to an invention nonelected with traverse in Paper No. 2/16/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Maintained rejections

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction

or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claim 4 encompasses a method of evaluating the possibility of onset or onset of rheumatoid arthritis (RA), by detecting the presence or absence of a gene encoding the protein of SEQ ID NO 1. Claims 7 and 8 are drawn to measuring the amount of mRNA derived from the whole angiopoietin-1 gene including wildtype angiopoietin 1 and "any" mutant angiopoietin 1. Claim 8 is drawn to the use of threshold values 1 and 2 to determine possibility of a subject developing RA.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches the insertion of GGT at positions 805-807resulting in a glycine being inserted into amino acid position 269 of SEQ ID NO.1 (see page 25, 1st full paragraph). The specification further teaches this insertion is depicted in SEQ ID NO. 2 (see page 25, line 10). The specification teaches a 3 base deletion (see page 10, line 11).

The specification teaches the homozygous or heterozygous deletion of "GGT" in SEQ ID NO. 2 occurs in 98.5% of subjects with familial history RA, diagnosed with RA (see Figure 4). The specification further teaches 100% subjects with familial history RA, not diagnosed with RA, were homozygous or heterozygous for deletion of "GGT" in

SEQ ID 2 (see figure 4). The specification further teaches 98.2% of subjects with sporadic RA were homozygous or heterozygous for the "GGT" deletion. While 100% of the subjects related to those diagnosed with sporadic arthritis have the homozygous or heterozygous "GGT" deletion.

The specification further teaches the patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) have RA: familial RA (1.5%) and sporadic RA (1.8%). The specification appears to teach patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) were found only with RA, but the homozygous or heterozygous "GGT" deletion was found both in subject with RA and those without RA. Thus it appears that an association exists for humans homozygous for the presence of "GGT" at position 805-807.

However, the claims are drawn to the insertion of a glycine as the 269th position of SEQ ID NO. 1 (SEQ ID NO1 teaches a glycine as the 269th amino acid), or the insertion of "GGT" at nucleotides 805 to 807 of SEQ ID NO.2 (SEQ ID NO2 teaches GGT at positions 05 to 807). It is thus unclear if the applicant wants the invention claimed, or the invention that appears to be taught.

In another study, the specification teaches a statistically significant reduction in mRNA as detected by a probe with sequence of SEQ ID NO.9 in patients (21) with RA compared with 18 controls (see figure 5). The specification does not teach if the RA patients are homozygous or heterozygous for the "GGT" insertion or deletion. Although this finding is statistically significant, the claims require analysis in relation to the first study and the ability to correlate this decreased mRNA with RA however is unclear. The

specification further teaches the use of threshold values 1 and 2 to evaluate if a subject is predisposed to RA or not (see page 31, 1st full paragraph). The specification further asserts this value should be set such that value 1 is set to equal or less then the average value of mRNA expression in RA patients (see page 30 1st full paragraph). The specification further asserts threshold value 2 should be set to be equal or more then the average value of mRNA expression for healthy individuals or "arbitrarily in other ways in accordance with the data of detection" (see page 29, lines 12-13).

The specification does not specifically define threshold values for 1 and 2. As the specification asserts threshold values 1 and 2 should be determined by use of averages for RA patients and healthy subjects, or arbitrarily, to evaluate the presence of a disease, let alone the onset of a disease without specific threshold values.

The state of prior art and the predictability or unpredictability of the art:

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 -

Discussion). The prior art of Newton et al (Journal of computational biology (2001) volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to determine if the claimed invention encompasses SEQ ID NO.1 with a glycine at positions 269 and 270, or a glycine at position 269, or no glycine at position 269 or 270, and the nucleic acids that correspond to these peptides. Experimentation would be replete with unpredictable trial and error analysis because the specification does not in clear, concise and exact terms describe the invention so as to allow the skilled artisan to make and use the invention as claimed.

The skilled artisan would then have to determine if the insertion as claimed was sufficient for the RA phenotype, or if as the specification asserts the lack of a deletion is correlated with RA. Further the skilled artisan would have to determine if this insertion or deletion taught by the specification is by itself sufficient for diagnosing RA onset, or as the specification shows requires homozygosity of "GGT" at position 805-807.

With respect to amended claim 7, the skilled artisan would further have to determine if "any" mutation in SEQ ID No1 or SEQ ID No2 is correlated with RA. This

would be unpredictable because the specification has only taught one mutation and the ordinary artisan could not extrapolated a structure function relationship to other mutations with humans or other species from this one example.

Further the skilled artisan would have to determine the threshold values 1 and 2 that would be indicative of expression of mRNA of SEQ ID NO.2 in such a way that as to determine if a patient had high or low expression of this nucleic acid molecule. As the specification does not define threshold values 1 and 2 and suggests they can be arbitrarily determined (see page 29, lines 12-13), it would be unpredictable to use these threshold values to predict a disease state.

Due to the scope of the claims, one of skill in the art would be required to further undertake unpredictable trial and error experimentation to make and use the invention as claimed.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response filed on 2/16/2007 asserts on page 6 the specification does adequately point out what the mutation of the invention encompasses. The newly amended claim 4 and arguments now adequately describe the mutation as the nucleic acid encoding SEQ ID No 1. However, the response further asserts wildtype protein

does not have a glycine at position 269. This appears to be contradicted by both SEQ ID NO 1 and 2 of the specification. SEQ ID NO 1, teaches glycines at position 269 and 270. Deletion of GGT as taught by the specification would result in a glycine at 269. Similarly deletion of the GGT at positions 805-807 of SEQ ID NO: 2, would result in GGT at that position and a glycine being encoded at that position. Regardless, because of the clarified claim language the claim clearly points out the detection of SEQ ID NO 1.

The response of 2/16/2007 on page 6 further asserts there is a significant difference between the presence of mutant gene and/or protein with RA patients from sporadic families and healthy subjects from sporadic families. This argument has been thoroughly reviewed but is not found persuasive. The response on page 6, asserts there is a significant difference between RA patients from sporadic families and healthy subjects from sporadic families however, the specification does not appear to teach a statistical difference between any groups in the studies of example 1 or figure 4. Further, the response does not teach or point to the p-value for the association study. The specification in figure 4, suggests that healthy subjects from families with familial RA are more likely to be heterozygous for the mutation (28.6%) than patients from families with familial RA (21.7%). This suggests that the heterozygous mutation is not predictably associated with familial RA as healthy family members possess the mutation as well. Further, patients with sporadic RA are heterozygous for the mutation 22.7% of the time, while healthy subjects related to the sporadic patients had the heterozygous mutation 7.8% of the time. This once again suggests that the heterozygous mutation is not indicative of RA. Finally the differences in the occurrence of the mutation in patients

with sporadic RA and healthy controls, as well as in patients with familial RA and healthy controls demonstrate that although the mutation appears to occur in both sporadic and familial RA, the mutation is present at different rates. If the mutation was predictably associated with "any" RA, the presence of the mutation would result in RA at similar rates in all subjects studied. As the healthy and diseased subjects patients have the mutation it is not clear if there is a significant association in any subject. As the presence of the mutation does not correlate with RA at similar rates in all groups it does not appear to be predictably associated with "any" RA, It is noted that although some arguments are drawn to mutant protein the nucleic acids are the claimed subject matter.

For claim 7, the response further asserts on page 7 asserts that RA patients have significantly smaller amounts of angiopoietin-1 mRNA compared to healthy controls. The response further asserts that mutant angiopoietin gene is associated with onset of RA and that threshold values are provided in the specification. This argument has been thoroughly reviewed but is not found persuasive. The specification teaches on page 30, that healthy subjects have mRNA values normalized to GAPDH from 0.095 to 0.5793 and RA patients range from 0.0049 to 0.1923. It appears that a human subject with an normalized mRNA amount of 0.095 to 0.1923 would fall in range for both RA patients and healthy subjects. It would be unpredictable to determine whether a patient was at risk of RA, if a patient was identified as having an mRNA value of 0.1 as values suggested in the specification for the RA patient and healthy ranges overlap. As the healthy and RA patient range overlap this causes unpredictability.

The response further asserts on page 7, that Wu and Newton are directed to the unpredictability of microarray analysis, while the instant invention is drawn to detection by quantitative PCR. Examiner agrees with this analysis.

New grounds of rejection Necessitate by Amendment

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In claims 7-8, the recitation "an mRNA derived from the whole Angiopoietin-1 gene, including wild-type angiopoietin-1 and mutant agiopoietin-1 gene in the subject" appears to be new matter. The specification does not provide basis for the concept of detecting an mRNA derived from angiopoietin-1 wildtype and "any" mutant. The specification teaches the use Taqman probe SEQ ID NO 9, to detect the expression of angiopoietin-1. The disclosure of a method of detecting angiopoietin-1 by use of Taqman probe of SEQ ID NO 9, does not support the detection of "any" angiopoietin.

7. Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claim 8 encompasses detection of "any" wildtype or mutant angiopoietin-1 gene. The claims do not set forth any functional requirements for mutations of angiopoietin-1.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches the insertion of "GGT" at position 805 to 807, which corresponds to the insertion of glycine at amino acid 269 of angiopoietin-1.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches nucleotide of SEQ ID 2, which is one species in the genus of "any" mutation of angiopoietin-1.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification teaches only 1 mutation, which is not representative of the genus claimed. The sequence of the insertion/deletion is not taught in such a way

that the skilled artisan could envision the structure claimed. Further, the specification does not teach a relationship between the structure of mutation and functional consequences of this mutation so the skilled artisan could determine from the disclosure of this single insertion/deletion, other associated mutations in humans or other species.

In the instant application, the provided information regarding "any" mutation of angiopoietin-1, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding "any" mutation of angiopoietin-1 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules the large genus of species encompassed by claims 7 and 8.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claim 7 is rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hillman et al (US Patent publication 2002/0123054, published 9/5/2002).

The MPEP 2111 teaches:

During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." >The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation".

Claim 7 is broadly drawn to a method of evaluating onset or possibility of onset of RA by the detection of an mRNA derived from "any" angiopoeitin-1 gene or "any" mutant.

Hillman et al teaches a method of diagnosing rheumatoid arthritis by the use of fragments of instant SEQ ID NO 2, which Hillman identifies as angiopoeitin (see paragraph 0089). Hillman thus teaches a method of detecting the onset or possibility of onset of RA by the detection of mRNA derived from "any" angiopoeitin-1 gene or "any" mutant.

Summary

No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEANNINE A. GOLDBERG
PRIMARY EXAMINER
4/26/07